Metabolic Complications Before and After Liver Transplantation

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In this chapter, we discuss metabolic complications such as diabetes, obesity, hypertension and dyslipidaemia in the population awaiting liver transplantation and in the liver transplant recipients. Metabolic syndrome and its components are associated with a higher risk of cardiovascular disease (CVD)-related morbidity and mortality in the perioperative period and in the short- and long-term post-transplantation. We provide evidence-based recommendations on the clinical management of each component of the metabolic syndrome. Herein, you will learn how to work up and manage such complications in patients listed for liver transplantation (LT) and in the transplanted population. We advocate that such comorbidities should be thoroughly assessed and aggressively treated in a context of a multidisciplinary team including metabolic physicians and dieticians with a special interest in transplantation.

20.1 Introduction

Survival following LT has been steadily improving over the last two decades, likely due to a greater surgical expertise, which reduced technical complications, a better selection of patients and improvements in the efficacy and tolerability of immunosuppressive therapy, reducing graft loss from both acute and chronic rejection. Conversely, cardiovascular morbidity and mortality is increasingly prevalent in liver transplant recipients as these patients now live longer. Moreover, an increasing number of patients listed for LT has metabolic comorbidities or NAFLD. Metabolic

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syndrome (MetS) is a common risk thread making the prevalence, prevention and management of pre- and post-transplant MetS and individual metabolic derangements of increasing interest and importance.

Metabolic syndrome is defined by the Adult Treatment Panel III criteria as the coexistence of three of the following features: (a) fasting glucose ≥110 mg/dL, (b) central adiposity, defined as waist circumference >102 cm in men or >88 cm in women, (c) hypertension, defined as systolic blood pressure ≥135 mmHg, diastolic blood pressure ≥85 mmHg or anti-hypertensive treatment, (d) serum triglycerides >150 mg/dL, and (e) serum HDL cholesterol <40 mg/dL in men or <50 mg/dL in women.

In Western world and developing countries, the prevalence of MetS is rising, in parallel with that of obesity, and NAFLD affects around 30% of the adult population [1, 2]. NAFLD is not only considered as the hepatic manifestation of MetS [3] but an independent risk factor for its development [4] and for CVD [5]. Notably, the prevalence of MetS in the cirrhotic population with non-alcoholic steatohepatitis (NASH) or chronic viral hepatitis (CVH) is significantly higher than that of the non-cirrhotic NASH/CVH population [6], and indeed, MetS has been hypothesized to play an active role in the progression of liver fibrosis [7–9]. NAFLD/NASH cirrhosis, moreover, has become one of the most frequent causes of chronic liver disease in developed and developing countries and is at present one of the leading indications for liver transplantation both for end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) [10, 11].

Metabolic comorbidities before and after LT negatively impact both the short- and the long-term outcome of liver transplant recipients [12, 13]. Therefore, it is reasonable to state that there is a need to thoroughly assess LT candidates for MetS and that NAFLD patients may need an even more in-depth cardiovascular screening. Accordingly, aggressive treatment should be adopted to improve the metabolic comorbidities of patients both in the waiting list and after LT.

- Obesity is an independent risk factor for decompensation in patients with cirrhosis, while metabolic comorbidities increase the perioperative transplant risk. Post-LT patients are at increased risk of cardiovascular morbidity even in the absence of pre-existing metabolic risk factors.

20.2 Metabolic Complication Assessment and Treatment Before LT

All LT candidates should undergo a careful cardiovascular evaluation before liver transplantation and metabolic complications should be treated. Based on the frequent presence of metabolic comorbidities, liver transplant candidates with NAFLD/NASH should be considered at high risk of developing cardiovascular events before and after LT [13] as these patients might have silent cardiovascular disease that can become clinically evident during and after surgery. Therefore, even though there is insufficient evidence to recommend a specific cardiovascular risk assessment for

NASH patients, the cardiovascular risk should be carefully assessed by a multidisciplinary team, which should include a cardiologist and an anaesthesiologist with special interest in transplantation [14].

20.2.1 Cardiovascular Risk Assessment

Cardiovascular events are the major cause of non-graft-related complications after liver transplantation, and therefore patients should be screened and treated for silent cardiovascular disease and for its risk factors. The presence of cardiovascular disease is not an absolute contraindication for liver transplantation, but needs to be carefully assessed in order to optimize the patient pre-LT.

An appropriate cardiovascular risk evaluation in patients with metabolic comorbidities should include screening for subclinical coronary artery disease (CAD) and should aim to either treat abnormal findings before surgery or deny transplantation to those whose risk is too high and would therefore likely not benefit from LT [15, 16].

All patients on evaluation for LT should undergo (1) witnessed timed climb of two flights of stairs with pre- and post-O_2 saturations, (2) 12-lead ECG and (3) trans-thoracic echo as these are reliable and easily performed tests for a first assessment of cardiac function. For patients who present abnormal findings in these tests and/or have additional coronary risk factors such as diabetes, obesity, hypertension and/or NAFLD, further testing with dobutamine stress echo (DSE) is recommended [14]. The sensitivity of DSE is reduced in most LT candidates with end-stage liver disease, because they may not be able to reach the target heart rate as a result of deconditioning and/or concurrent beta-blocker therapy. However, its high specificity/negative predictive value makes DSE an efficient tool for an estimate of perioperative and long-term cardiac events in this population [17]. On the basis of DSE results, it is possible to select patients for which a non-invasive (CT scan coronary angiography) and/or invasive assessment of CAD with coronary angiogram might be warranted. However, such decisions should be made following multidisciplinary discussions, as revascularization of silent CAD may not be beneficial or offer survival advantage [18]. For instance, a 50% post-transplant mortality after revascularization in patients with severe CAD has been described [19].

Additional tests that might be useful are cardiopulmonary exercise testing (CPET) and the 6-minute walking test (6MWT) as they predict early post-transplant survival [20, 21]. Similarly coronary artery calcium score has been shown to be predictive of obstructive CAD and of one-month cardiovascular complications after LT [22].

Currently, absolute contraindications for LT are non-revascularized obstructive severe multi-vessel CAD, left-ventricular ejection fraction <40%, moderate-to-severe right heart failure, severe pulmonary hypertension associated with right heart failure and/or not responsive to medical treatment, recurrent ventricular arrhythmias, severe irreversible valvular disease and congenital heart disease associated to severe right heart failure unresponsive to medical therapy [23].

20.2.2 Hypertension, Dyslipidaemia and Diabetes Mellitus

Each traditional cardiovascular risk factor should be treated, and medical strategies, including diet, physical activity and pharmacotherapy, should be maximized before LT.

Most patients with advanced cirrhosis have low arterial pressure; therefore, the need for anti-hypertensive treatment decreases as cirrhosis progresses. Non-cardioselective beta-blockers are the preferred option for treating hypertension in the LT waiting list, as these are effective drugs for both arterial and portal hypertension [24]. There is increasing evidence on the safety of beta-blockers in patients with ascites (including refractory ascites) provided treatment is stopped in the presence of a low mean arterial pressure, and they are reinitiated once mean arterial pressure re-increases and/or contraindicating conditions are solved [25, 26]. Alternatively, if a patient has comorbidities that contraindicate beta-blockers or does not tolerate them, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) can be safely used if there is no ascites and no concomitant impaired renal function [27, 28]. When beta-blockers are indicated to prevent or treat CAD, cardioselective beta-blockers such as bisoprolol, metoprolol and carvedilol can be a valid option [29–31].

With regard to diabetes, in patients with compensated cirrhosis, standard treatment as per international guidelines is recommended, with metformin used as first-line treatment. Specifically for patients with NAFLD/NASH cirrhosis, pioglitazone has demonstrated efficacy both in diabetes mellitus (DM) treatment and in improving NASH-histological features and would be a reasonable second-line treatment choice [32, 33]. Potential side effects of pioglitazone are weight gain due to peripheral oedema and a small risk of congestive heart failure. Glucagon-like peptide 1 agonists, such as liraglutide, can help with weight loss and could be used in obese patients [34].

In the context of decompensated cirrhosis, the first-line treatment is insulin even if, unless there is a specific contraindication, metformin can also be safely used [35]. Furthermore, some studies suggest a protective role of metformin in reducing the risk of HCC occurrence [36].

As regards dyslipidaemia, cholesterol levels decrease in patients with worsening synthetic function; therefore, there is no need for treatment in most patients with Child Pugh C cirrhosis. For patients with hyperlipidaemia, the first-line treatment is statins. Their beneficial impact on preventing CAD is widely known; furthermore, there is increasing evidence about their effects on improving portal hypertension and all-cause mortality in cirrhosis and on HCC prevention [37, 38]. Use of statins is safe in patients with Child Pugh A cirrhosis. Dose reduction might be required in Child Pugh B and C as increased incidence of rhabdomyolysis has been reported in such patients.

20.2.3 Renal Dysfunction

MetS features are risk factors for chronic kidney disease (CKD). A degree of functional renal dysfunction (type 2 hepatorenal syndrome) is present with increasing

severity of liver disease and increases overall mortality [39]. NAFLD and chronic kidney disease (CKD) are strongly associated [40] and share common pathogenetic pathways [41]. It is often a challenge to differentiate CKD from type II hepatorenal syndrome in patients with cirrhosis and metabolic comorbidities. Therefore, screening for renal dysfunction in all patients with end-stage liver disease is mandatory, most of all if MetS or some of its features coexist.

Importantly, CKD is a risk factor not only for morbidity and mortality in end-stage liver disease but also for post-transplant CVD and mortality [23]. Consequently, it is desirable to prevent kidney function deterioration by treating risk factors (hypertension, diabetes, dyslipidaemia, and obesity) and consider simultaneous liver-kidney transplantation when required (i.e. when eGFR is lower than 30 ml/min due to CKD).

20.2.4 Obesity and Malnutrition

The global epidemic of obesity is reflected in both the growing burden of NAFLD and the increasing number of obese patients with cirrhosis. Importantly, the presence of obesity is an independent risk factor for decompensation in stable patients with cirrhosis [42]. A pilot study showed that 16 weeks of diet and moderate exercise were safe and effective to reduce body weight and portal pressure in obese cirrhotic patients with portal hypertension [43].

Obesity may have a negative impact on short- and long-term outcomes after LT. There have been several studies reporting conflicting results on the effects of obesity on post-LT outcomes with some of them even showing a survival benefit after LT [44, 45]. In a recent analysis of the UNOS database from 1987 through 2007, among 73,538 LT recipients, extreme BMI (<18.5 kg/m^2 and >40 kg/m^2) was a significant predictor of death after LT [46]. The negative impact of BMI seems to be even higher in conjunction with the severity of liver disease or associated comorbidities, especially with diabetes which conferred a four-fold increase in the risk of infections, cardiovascular events and acute renal failure [47, 48]. Additionally, severe obesity (BMI >40 kg/m^2) was an independent predictor of death not only in the post-operative period but also at 1, 3 and 5 years after LT [49]. Not surprisingly, because of the abovementioned higher prevalence of complications, an increase in the length of hospital stay in obese patients with NASH, up to 50%, has been reported [50].

Given the conflicting results about BMI and post-LT risk, it has been suggested that BMI alone is not a satisfactory tool to stratify the risk of obesity, and that visceral adipose tissue and muscle mass are parameters that should be added to complete an adequate pre-transplantation evaluation [51]. The latter suggestion gives relevance to the increasingly recognized problem of sarcopenic obesity, that is, of obese patients with sarcopenia, who might be at greater risk of complications.

Nutrition is an integral part of patient care before LT as nutrition status and specifically sarcopenia is related to morbidity, mortality and length of hospital stay

[52]. Around 25% of obese patients suffer from malnutrition [53]. All LT candidates should adopt lifestyle modifications including physical exercise in order to preserve muscle mass [54], in conjunction with diet if they are obese. This should be made in a context of a multidisciplinary team including a dietician with special interest in cirrhosis. Pragmatically, a validated tool for a nutritional assessment in cirrhotic patients is the Royal Free Subjective Global Assessment that recognizes three categories of patients: well nourished, mild/moderately malnourished and severely malnourished [55] and helps deciding which patients need nutritional advice. Generally, cirrhotic patients should follow a high calorie (25–35 kcal/kg/day) and high protein regimen with 1.2/1.5 g/kg of proteins daily. They should also avoid fasting and aim for 4–7 meals per day including a late night snack are recommended. Cirrhotic patients with obesity are at high risk for depletion of various fat- and water-soluble vitamins and trace elements and should be supplemented appropriately [56].

A personalized, adapted physical activity programme based on cyclo-ergometry plus muscle strengthening according to ventilatory threshold for 12 weeks demonstrated to be safe and feasible in patients awaiting LT [57].

Bariatric surgery at the time of LT or post-operatively has the potential to not only improve obesity-associated conditions, such as diabetes, but also the potential to influence the incidence of NASH in the post-LT setting. However, there continues to be no consensus on the use and timing of bariatric surgery in this patient population [58]. When considering bariatric surgery before LT, Child-Pugh A patients with no portal hypertension could be evaluated, whereas this is contraindicated in Child B and C cirrhosis due to unacceptably high mortality [59].

20.3 Metabolic Syndrome After Liver Transplantation

The reported prevalence of MetS after liver transplantation varies from 45% to 58%, which is more than twice the prevalence in the general population [60]. Specifically, among LT recipients, 10%–64% develop type 2 diabetes mellitus, 45%–69% experience hyperlipidaemia, and approximately more than 50% develop hypertension. Not surprisingly, high rates of recurrent and de novo NAFLD can be found after LT, in up to 30% of transplant recipients [61–64]. These findings are relevant as NAFLD and MetS increase the risk of CVD.

LT recipients are at increased risk of MetS and cardiovascular morbidity and mortality even in the absence of pre-LT risk factors [65] and are at higher risk of CVD in comparison to general population [66]. This is basically related to weight gain (as patients feel better and eat more after surgery) and immune-suppressive drugs, which confer a higher risk of DM, hypertension and dyslipidaemia. Long-term use of corticosteroids is associated with de novo diabetes, hypertension and dyslipidaemia. Moreover, calcineurin inhibitors (CNIs) may negatively impact metabolism as they favour weight gain [67] and the onset of hypertension and diabetes [68, 69]. Patients treated with mammalian target of rapamycin (mTOR)

inhibitors were at higher risk of hyperlipidaemia and glycaemic alteration with respect to patients under CNIs [70]. However, mTOR inhibitors induce less weight gain in comparison to CNIs [71].

Similarly to the pre-LT setting, the presence of metabolic abnormalities increases the risk of CVD and therefore needs to be aggressively treated.

20.3.1 Cardiovascular Risk

Among non-graft-related causes, CVD is the leading cause of morbidity and mortality independently from the aetiology of liver disease requiring LT. Overall, CVD accounts for 11% of deaths at 1 year among LT patients, followed by infections (9%) and renal failure (6%) [72]. Furthermore, cardiovascular events remain one of the leading causes of morbidity and mortality also at long-term follow-up with a reported cumulative increasing incidence at 15.3%, 20.7% and 30.3% years post-LT at 3, 5 and 8 years post-LT, respectively; CVD is predominantly represented by coronary artery disease and myocardial infarction [73, 74]. Although the overall survival among patients transplanted for NAFLD is the same as for patients transplanted for other aetiologies [75], NAFLD patients are at higher risk of cardiovascular morbidity [76, 77].

The principal risk factors identified so far for major cardiovascular events (i.e. stroke, myocardial infarction, transient ischemic attack, sudden death and acute coronary syndrome) in the transplanted population are post-transplant MetS [78], male sex, pre-LT cardiovascular disease, older age at LT, diabetes, post-transplant hypertension [77, 79] and renal dysfunction [23, 80]. Therefore, the clinician should aim at treating appropriately each one of these risk factors.

20.3.2 Hypertension, Diabetes and Dyslipidaemia

Arterial hypertension affects up to 70% of transplant recipients [81] and is secondary to immunosuppressive agents, primarily corticosteroids and calcineurin inhibitors. CNIs can lead to hypertension due to systemic and renal arterial vasoconstriction, reduced vasodilation (due to lower nitric oxide production) and increased sodium retention [82]. Therefore, before introducing anti-hypertensive drugs, steroids should be stopped if possible, while the CNIs dose should be titrated at the minimum effective dose, unless otherwise indicated. If necessary, a CNI sparing strategy with the addition of mofetil mycophenolate (MMF) or azathioprine (AZA) can be considered. If these strategies are insufficient to reduce blood pressure, then calcium channel blockers (CCBs), such as amlodipine or nifedipine, are the first-line choice as they counteract CNI-related renal arteriolar vasoconstriction and reduce systemic vascular resistance. β-Blockers are second-line agents and have similar efficacy to CCB. ACE-I and angiotensin-receptor blockers (ARB) are of limited value when used as monotherapy for hypertensive patients early after LT as plasma

renin activity is low during this period; furthermore, they may magnify collateral effects of CNIs such as hyperkalaemia and metabolic acidosis. However, they can be used further down post-LT, when the activation of the renin-angiotensin system becomes more evident, and are the first-line option for patients with CKD, DM and/or proteinuria [74]. The use of diuretics is debatable and requires electrolyte monitoring due to potential electrolyte disturbances [83]. The goal of anti-hypertensive treatment is blood arterial pressure less than 130/80 mmHg. If such values cannot be reached with monotherapy, combinations of CCB and ACE inhibitors or ARB can be considered.

The development of DM is multi-factorial. An increased incidence in patients transplanted for HCV or with DM pre-LT in obese, black Afro-American patients and in male gender is reported. As for hypertension, the choice and dose of immunosuppressive medications are the major modifiable risk factor [84]. Corticosteroids should be rapidly tapered and discontinued unless otherwise needed. CNIs can cause diabetes due to direct damage to pancreatic islet cells; therefore, their dose should be minimized as soon as possible; this improves long-term outcomes with no adverse effects to graft survival [85]. Tacrolimus has a greater diabetogenic effect compared to ciclosporin [86]; however, switching from tacrolimus to ciclosporin is not recommended due to inferior graft outcomes. Otherwise, a sparing strategy reducing CNIs with the addition of MMF/AZA can be considered. Currently, no specific recommendations exist about treatment of DM on transplanted population; therefore, standard treatment should be undertaken with the aim of target glycosylated haemoglobin <7%, fasting blood sugar of 70–130 mg/dL and peak postprandial glucose <180 mg/dL [87].

Dyslipidaemia occurs in up to 70% of liver transplant recipients [88]. Again, immune suppressants play a role in its pathogenesis. Long-term corticosteroid use is a well-established cause of hyperlipidaemia. With regard to CNIs, cyclosporine is associated with more frequent hyperlipidaemia and hypertriglyceridemia compared to tacrolimus; this could be related to inhibition of bile salt synthesis [89]. Sirolimus is associated with high rates of dyslipidaemia as well; this might result from changes in insulin signalling pathways resulting in excess triglyceride production and secretion [90]. Therefore, a pragmatic approach is to avoid long-term corticosteroids and sirolimus in patients with hyperlipidaemia. Post-transplant dyslipidaemia is generally resistant to dietary interventions; therefore, statins are first-line treatment as they are safe, efficacious and well tolerated [91]. Pravastatin is the most studied and used because it has no interaction with immunosuppression therapy. Ezetimibe can be used as well in patients not sufficiently treated with statins [92]. Ezetimibe monotherapy is ineffective and should be avoided. Hypertriglyceridemia responds to fish oil (ω-3), and since very few side effects and drug interactions can be expected, this is the first-line option. Alternative agents are fibrates, which are generally well tolerated but may have a mild effect on increasing CNI serum levels. For this reason, it is not recommended to prescribe statins and fibrates contemporarily for patients under CNIs. The treatment goal for

dyslipidaemia is obtaining LDL values below 100 mg/dL and triglycerides below 150 mg/dL [93].

20.3.3 Obesity

Obesity is a very frequent complication in the transplanted population secondarily to increased appetite and food consumption, reduced catabolism and immunosuppressive treatment. Not surprisingly, the potential impact of post-LT weight gain includes increased risk of DM, and MetS and its associated complications, such as CVD, renal disease and de novo NASH in the allograft. Steroids induce weight gain; therefore, minimizing their dosage is advisable. Similarly to the pre-LT setting, the management of obesity in the post-LT period is mainly based on lifestyle modifications with a hypocaloric diet, combined with aerobic physical activity. Only orlistat, a reversible inhibitor of pancreatic lipase, has been investigated in the post-LT setting and appears to be of limited efficacy and with the additional burden of potentially interference with IS drug absorption [94]. Only few cases of bariatric surgery are reported; it appears to be well tolerated and successful, although to re-operate a LT recipient can be complex and can impact future access to the biliary tree.

Case Study A 62-year-old female of Indian origin transplanted in 2009 for NASH cirrhosis presents with a weight of 68 kg, a BMI of 28 kg/m^2 and blood pressure of 140/80 mmHg. Comorbidities are T2DM, hypertension and hyperlipidaemia. Blood test shows: HbA1c 6.5%, LDL cholesterol 150 mg/dL, AST 45, ALT 40, creatinine 1.5 mg/dL and trough tacrolimus levels 3 ng/mL. At a biopsy from 2015, recurrence of cirrhosis is evidenced. Medications include tacrolimus 2 mg BD, MMF 500 mg BD, metformin 1 g BD, losartan 50 mg BD and atorvastatin 10 mg OD.

What would you do?

1. Decrease tacrolimus and increase MMF
2. Add amlodipine
3. Increase atorvastatin
4. Add another anti-diabetic agent
5. 2 and 3
6. All the above

Based on the current recommendations, the best approach would be to decrease tacrolimus and increase MMF as a renal sparing strategy; moreover, amlodipine should be added to effectively control hypertension. The LDL levels are suboptimal; therefore, atorvastatin dosage should be increased. For diabetes, another anti-diabetic agent should be added as well.

▶ Metabolic comorbidities are often overlooked in the post-LT setting. Small interventions can significantly reduce the cardiovascular risk of recipients (Table 20.1).

Table 20.1 Treatment of metabolic syndrome before and after LT. This table summarizes current pharmacologic interventions that need to be added to lifestyle modification, physical activity and immunosuppressive minimization post-liver transplant

Treatment of metabolic syndrome		
	Before LT	After LT
Hypertension	Beta-blockers first-line option ACEI or ARB in case of CAD and/or CKD (should be avoided in decompensated patients)	CCB is first-line treatment Beta-blockers are second-line treatment ACEI in case of concomitant CKD and/or diabetes in long-term post-LT setting
Diabetes	In compensated patients: Metformin first line, consider adding pioglitazone or liraglutide if NASH Decompensated patients: Metformin but requires close monitoring, otherwise insulin	Standard treatment as per international diabetes guidelines (metformin first line)
Dyslipidaemia	Statins	Statins (pravastatin preferred as it has no interaction with CNIs) Ezetimibe can be added. Omega 3 acids first line for hypertriglyceridemia
Obesity	Diet with the support of an expert dietician Bariatric surgery can be considered in child A patients	Diet with the support of an expert dietician

LT Liver transplantation, *CCB* Calcium channel blockers, *ACEI* Angiotensin-converting enzyme inhibitors, *ARB* Angiotensin receptor blockers, *CAD* Coronary artery disease, *CKD* Chronic kidney disease, *CNIs* Calcineurin inhibitors

Key Points

Before liver transplantation:

- Obesity is an independent risk factor for decompensation in stable cirrhosis.
- Child A cirrhosis offers a window of opportunity for interventions in metabolic comorbidities and reduction of the cardiovascular risk.
- A thorough cardiovascular assessment is required as well as aggressive treatment of comorbidities in the pre-transplant evaluation of patients.

After liver transplantation:

- Recognize cardiovascular risk factors early with a complete yearly blood screening for DM and dyslipidaemia and monitoring of weight and blood pressure at each visit.
- Pharmacologic treatment is recommended for hypertension, diabetes and dyslipidaemia besides lifestyle modification and physical activity.
- Minimizing CNIs dose after the first year is advisable to reduce metabolic side effects.

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